IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF Engel *et al.* Confirmation No.: 5040

Application No.: 09/523,455 Group Art Unit: 1617

Filed: March 10, 2000 Examiner: Carter, Kendra D.

Title: METHOD FOR A PROGRAMMED CONTROLLED OVARIAN STIMULATION PROTOCOL

MAIL STOP APPEAL BRIEF–PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Appellants file this Appeal Brief pursuant to 37 C.F.R. § 41.37, in support of their Notice of Appeal, dated May 9, 2011. These papers are due on or before September 9, 2011, with a two-month extension of time. Additionally, Appellants submit concurrently herewith a Request for Oral Hearing and the fee for filing this Request as required under 37 C.F.R. § 41.20(b)(3).

Appellants do not believe any additional fees are due. However, the Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to Deposit Account No. 033975, Reference No. 098501-0264671.

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I. Statement of Real Party In Interest

The real party in interest is AEterna Zentaris GmbH.

II. Statement of Related Cases

Appellants know of no other related cases, including any related applications, appeals or interferences, which will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

III. Status Of Claims

Claims 4-9 and 16-28 are pending, rejected as set forth in the *Final Office Action* of January 4, 2011, and the subject of this appeal. Claims 1-3 and 10-15 are canceled. Claim 26 is the sole independent claim.

IV. Status of Amendments

No claim amendments were submitted after the *Final Office Action*.

V. Summary of the Claimed Subject Matter

The present invention relates to methods for therapeutic management of infertility and increasing the quality of fertilized oocytes and embryos by programming controlled ovarian stimulation (COS) and assisted reproductive techniques (ART) in order to optimize oocyte harvesting and fertilization during the clinical week of Mondays to Fridays. The claims recite a first use of LHRH antagonists for the purpose of programming the beginning of the menstrual cycle. This is accomplished by administering the LHRH antagonist in the late leutal phase for the purposes inducing

leutal regression — that is, ending the previous normal menstrual cycle via luteolysis. Once the menstrual cycle is reset, physicians are benefited with the ability to control the timing of ovarian stimulation and fertilization of the eggs using assisted reproductive techniques. See *e.g.*, Declaration under §1.132 by Dr. Riethmuller-Winzen, inventor, submitted December 13, 2005.

The claims are directed to an IVF program that includes the step of administering the LHRH antagonist in the late leutal phase in conjunction with known treatment controlled ovarian stimulation (COS) and assisted reproductive techniques (ART) procedures. These procedures typically involve the use of follicle-stimulating hormone (FSH) and human menopausal gonadotropin (HMG) for the purposes of controlled ovarian hyperstimulation (*e.g.*, with FSH) and controlled induction of ovulation and final follicle maturation (*e.g.*, with HMG), and also the known use of LHRH antagonists for prevention of a premature luteinizing hormone (LH) surge.

The present claims thus require a first use of LHRH antagonists, for the purpose of programming the beginning of the menstrual cycle, and a second use of LHRH antagonists, for the purposes of preventing a premature LH surge. This second use of LHRH antagonists is according to known treatment protocols. For example, a LHRH antagonist may be "administered to prevent LH surges on day 5 until and including the day of ovulation induction with HCG." See *Specification* at page 1, lines 25-27.

Claim 26 is the sole independent claim. Claim 26 recites a method of programming an infertility treatment cycle comprising controlled ovarian stimulation (COS) and assisted reproductive techniques (ART). As provided in claim 26, the method comprises, *inter alia*, the following:

1. administering a first dose regimen of an LHRH antagonist during said luteal phase of said first menstrual cycle, wherein said first dose regimen of LHRH antagonist induces a luteal regression (support for this element may be found in the *Specification*, *inter alia*, at page 3, lines 30-33; page 4, lines 13-14; and original claims 16-20); and

2. administering a second dose regimen of said LHRH antagonist during said follicular phase, wherein said second dose regimen of an LHRH antagonist suppresses premature ovulation (support for this element may be found in the *Specification*, *inter alia*, at page 4, lines 5-8 and original claim 1).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following issues are on appeal:

Whether the rejection of claims 4, 5, 7, 16, 18, 21, and 25-28 under 35 U.S.C. §103(a) over *Felberbaum*[1] or *Olivennes*[2] in view of *Ziegler*[3] and *Hall*[4] is proper.

Whether the rejection of claims 22-24 under 35 U.S.C. §103(a) over *Felberbaum* or *Olivennes* in view of *Ziegler and Hall* and further in view of *Garfield*[5] is proper.

Whether the rejection of claims 6, 8, 9,17,19, 20 and 27 under 35 U.S.C. 103(a) over *Felberbaum* or *Olivennes* in view of *Ziegler* and *Hall* and further in view of *Deghengi*[6] or *Rabasseda*[7] is proper.

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1 R. FELBERBAUM et al., 'Multiple dose protocol for the administration of GnRH-antagonists in IVF: the "Lubeck-protocol"', 10th WORLD CONGRESS ON IN VITRO FERTILIZATION AND ASSISTED REPRODUCTION, May 1997, pp. 397-404.

2 Olivennes et al., The Single or Dual Administration of the Gonadotropin-releasing Hormone Antagonist Cetrorelix in an In Vitro Fertilization-Embryo Transfer Program, 1994, Fertility and Sterility, 62(3), pages 468476.

3 Ziegler et al., Synchronization of Endogenous and Exogenous FSH Stimuli in Controlled Ovarian Hyperstimulation (COH), 1998, Human Reproduction, 13(3), pages 561-564.

4 Hall et al., Variable Tolerance of the Developing Follicle and Corpus Luteum to Gonadotropin-Releasing Hormone Antagonist-Induced Gonadotropin Withdrawal in the Human, 1991, Joumal of Clinical Endocrinology and Metabolism, 72(5), pages 993-1000.

5 U.S. Patent No. 5,470,847.

6 U.S. Patent No. 5,945,128.

7 Rabasseda et al., Drugs of the Future, 24:393-403 (1999).

VII. Statement of Facts

A. Teachings from the primary references: *Felberbaum* and *Olivennes*

Gonadotropin-releasing hormone (GnRH) is also known as luteinizing-hormone-releasing hormone (LHRH). *Felberbaum* discloses that second generation GnRH antagonists (*i.e.* Cetrorelix and Ganirelix) can be administered in an *in vitro* fertilization (IVF) program to avoid premature LH-surges, an improvement over first generation GnRH antagonists. The IVF program taught in *Felberbaum* involves stimulation with human menopausal gonadotropin (HMG) started on cycle day 2, then from day 7 until induction of ovulation by human chorionic gonadotrophin (hCG), Cetrorelix is administered in daily fashion.

Olivennes teaches an IVF program having the same steps of *Felberbaum*, as is explained on pages 4 and 5 of the *Final Office Action.*

Felberbaum does not disclose administering an LHRH antagoinist (*e.g.*,Cetrorelix) during the luteal phase of a first menstrual cycle, as is acknowledged by the Examiner of page 5 of the *Final Office Action. Felberbaum* does not disclose inducing luteal regression by any means.

Olivennes also does not disclose administering an LHRH antagoinist (*e.g.*,Cetrorelix) during the luteal phase of a first menstrual cycle, as is acknowledged by the Examiner of page 5 of the *Final Office Action. Olivennes* does not disclose inducing luteal regression by any means.

B. The Teachings of the Secondary Reference: *Ziegler*

Ziegler discloses an IVF program that does not use LHRH antagonists (*e.g.,* Cetrorelix and Ganirelix). Rather, *Ziegler* teaches the administration of oestradiol to permit an advanced timing of the onset of controlled ovarian hyperstimulation treatments (*e.g.*, FSH administration and treatment used in conventional IVF therapies). See *e.g.*, *Ziegler* at Abstract. Oestradiol is not an LHRH antagonist. *Ziegler* does not teach administering an LHRH antagonist (*e.g.*,Cetrorelix) during the luteal phase of a first menstrual cycle.

Ziegler describes a method for "timing assisted reproductive techniques (intrauterine insemination and in-vitro fertilization) in the natural cycle" that comprises administering estradiol starting about 7 days before the onset of menses and continuing for about 5 days, until the first Tuesday following the onset of menses, defined as functional day (FD) 0; starting daily administration of HMG on FD3 (Friday) that is continued for about 11 days, on average, of HMG treatment; and then administering HCG to induce ovulation. The method of *Ziegler* delays the intercycle elevation of FSH but does not affect the timing of the onset of menstrual bleeding, which is described as being regulated by progesterone (*see* page 562, right column). *Ziegler* expressly describe their method as one that permits an advanced timing of the onset of controlled ovarian hyperstimulation (COH) treatments "when gonadotrophin-releasing hormone (GnRH) agonists are not used," and as having practical applications for timing ART "in the natural cycle." *See* page 561, left column.

Ziegler does not disclose inducing luteal regression by any means. The purpose of administering oestradiol was to achieve the desired outcome, which is to

"synchronize the increase in endogenous FSH with the onset of human menopausal gonadotropin (HMG) treatment." *Ziegler* at Abstract. *Ziegler* explains that in controlled ovarian hyperstimulation, "exogenous gonadotrophins are administered to amplify and sustain the gonadotrophic stimulus in order to prevent single follicular dominance by rescuing the rest of the cohort of follicles from atresia and hence achieve multiple ovulation." *Ziegler* at page 561, right column. In this manner, *Ziegler* promotes this approach as an alternative to the use of GnRH agonists, such as LHRH agonists. See *e.g.*, *Ziegler* at page 563, left column (stating that "[o]ur present protocol in which the timing of intercycle increase in FSH is controlled with physiological amounts of oestradiol… provides the same practical advantages without the complexity, the cost and the increased risk of ovarian hyper stimulation inherent to the use of GnRH agonists.").

C. The Teachings of the Secondary Reference: *Hall*

Hall is not related to an IVF program. *Hall* merely discloses the results of experiment designed to examine the differential sensitivity of the ovary to temporary withdrawal of gonadotropin support at different stages of folliculogenesis and corpus luteum function. See *Hall* at Abstract. *Hall* shows that the developing ovarian follicle varies in its tolerance to gonadotropin withdrawal, and the dominant follicle becomes increasingly controlled by local factors during late follicular phase and more resistant to short-term gonadotropin deprivation. With regard to the luteal phase, *Hall* concludes that a 72-hour GnHR receptor blockade is not tolerated by the corpus luteum and results in luteolysis.

Hall dose not disclose the use of GnRH antagonists in an IVF program. *Hall* does not disclose inducing luteal regression as part of an IVF program.

D. The Teachings of the Secondary Reference: *Garfield*

Garfield does not teach the use of LHRH antagonists for resetting the menstrual cycle to program COS and ART procedures. *Garfield* describes extensively physiologic and endocrine conditions and feed-back mechanisms (*see* col. 2 lines 9-17) as well as substances and procedures for the prevention of conception or ovulation in a physiologic non-manipulated menstrual cycle, *i.e.*, for the prevention of the implantation of a viable embryo and thus of pregnancy (*see* col. 1 lines 9-17). Additionally, *Garfield* does not teach the use of any substance for the resetting of the menstrual cycle for purposes of programming the COS and ART procedures or for ovarian stimulation.

E. The Teachings of the Secondary Reference: *Deghenghi*

Deghenghi discloses the process for manufacturing a pharmaceutical composition for the delivery of an effective amount of several LHRH antagonists amongst other bioactive peptides or peptide analogs (col. 2 lines 19-23), but does not teach the use of progesterone, LHRH antagonists, or contraceptive preparations for the programming of COS and ART procedures.

F. The Teachings of the Secondary Reference: *Rabasseda*

Rabasseda is described by the examiner as teaching that LHRH antagonists such as cetrorelix, ganirelix, and abarelix were known to be useful for treating female infertility. This is undisputed.

VIII. ARGUMENT

A. The Final Office Action Establishes No Apparent Reason or Motivation to Modify Teachings of the Cited References

An invention

> "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art…. [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418 (2007).

The Examiner, however, has provided no reason why the ordinary artisan would have chosen to administer an LHRH antagonist during the luteal phase of the menstrual cycle to induce luteal regression. As acknowledged by the Examiner on pages 4 and 5 of the *Final Office Action*, neither of the primary references of *Felberbaum* and *Olivennes* disclose administering an LHRH antagoinist (*e.g.*,Cetrorelix) during the luteal phase of a first menstrual cycle to induce luteal regression. The examiner relies on the teachings of *Ziegler* and *Hall* to established obviousness for these elements of the claims. In this regard, the Examiner merely contends that *Ziegler* teaches the desirability of administering "a composition during the luteal phase of one period and to allow for advanced scheduling of treatments to the next period." *Final Office Action* at page 6. The "composition" administered in *Ziegler* is oestradiol, which is not a LHRH antagonist. The "treatments" relate to ovarian hyperstimulation treatments, where *Ziegler* suggests that advanced oestradiol administration can help "synchronize the increase of endogenous FSH treatment with the onset of human menopausal

gonadotropin (HMG) treatment,"[8] which is not the same as inducing luteal regression as required by the claims. This rationale only addresses the timing element of the claims and is not specific to the composition or the results to be achieved. That is, the examiner's conclusion suggests that the administration of any composition in the luteal phase for the purpose of achieving any outcome would have been obvious. This rationale is thus insufficient to establish a *prima facie* case of obviousness.

Further, there is no scientific explanation or reasonable rationale set forth to support the desirability to substitute the administration of oestradiol, as disclosed in *Ziegler*, with an a LHRH antagonist. Indeed, the desired outcome achieved in *Ziegler* is not related to the subject matter of the present claims. *Ziegler* teaches administering oestradiol to "synchronize the increase in endogenous FSH with the onset of HMG treatment." *Ziegler* at Abstract. In this manner, *Ziegler* promotes this approach as an alternative to the use of GnRH agonists, such as LHRH agonists. See *e.g.*, *Ziegler* at page 563, left column. *Ziegler* does not disclose inducing luteal regression nor does *Ziegler* teach or suggest the desirability of inducing luteal regression as part of an IVF program.

Hall does not cure these deficiencies of *Ziegler*. *Hall* is not related to an IVF program. *Hall* merely discloses the results of experiments designed to examine the differential sensitivity of the ovary to temporary withdrawal of gonadotropin support at different stages of folliculogenesis and corpus luteum function. In this regard, *Hall* concludes that gonadotropin withdrawal is not tolerated by the corpus luteum and results in luteolysis. However, *Hall* makes no predications about the utility or safety of

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[8] *Ziegler* at Abstract.

this finding in IVF therapy. The examiner's reliance on *Hall* is speculative and made with the benefit of hindsight. This is improper.

Further, the examiner's rationale for combining *Ziegler* and Hall is that "*Ziegler* teaches the desirability of permitting the advanced timing of COH treatments by starting the administration of a composition during the luteal phase of one period and to allow for advanced scheduling of treatments to the next period." *Final Office Action* at page 6. According to the examiner, Ziegler teaches the administration of a composition during the luteal phase of one period and to allow for advanced scheduling of treatments to the next period and Hall teaches that an LHRH antagonist can induce luteal regression. However, the examiner's rationale merely establishes that the references can be combined and lacks a reason or motivation to combine. This is improper.

Moreover, there is no evidence that routine experimentation would have suggested administering an LHRH antagonist during the luteal phase of the menstrual cycle to induce luteal regression. The examiner has not even demonstrated inducing luteal regression as a known desired outcome in IVF therapy. Thus, the examiner has not even established that the results achieved in the cited references could have been optimized to result in the method now claims. Again, the examiner's rationale lacks a reason or motivation to combine.

The evidence of record does not support the examiner's position that an ordinary artisan would have considered the claimed processes obvious in view of *Felberbaum* or *Olivennes* in combination with *Ziegler* and *Hall*. The critical difference between the claimed invention and the cited prior art is the administration of an LHRH antagonist during the luteal phase of the menstrual cycle and induction of luteal regression

preceding the cycle of controlled ovarian stimulation (COS) therapy and assisted reproductive techniques (ART) procedures. The examiner has failed to clearly articulate a reasonable rationale for supporting the rejections set forth under 35 U.S.C. §103(a).

Appellants request that the rejection be reversed.

B. *Garfield* fails to cure the deficiencies of *Felberbaum* or *Olivennes* in view of *Ziegler* and *Hall*

Claims 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Felberbaum* or *Olivennes* , in view of *Ziegler*, and further in view of *Hall*, and further in view of *Garfield* . The inapplicability of *Felberbaum*, *Olivennes*, *Ziegler*, and *Hall* was discussed above. The Examiner cites *Garfield* as teaching clomiphene as a non-steroidal anti-estrogen. However, the present invention relates to LHRH antagonists not to estrogens or to anti-estrogens. Moreover, *Garfield* does not relate to the missing teaching, the administration of an LHRH antagonist during a first luteal phase to induce the timing of a second menstrual cycle. Accordingly, *Garfield* fails to cure the deficiencies of *Felberbaum*, or *Olivennes* in view of *Ziegler* and *Hall*.

C. *Dehgenghi* and *Rabasseda* fail to cure the deficiencies of *Felberbaum* or *Olivennes* in view of *Ziegler* and *Hall*.

Claims 6, 8, 9,17,19, 20 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Felberbaum* or *Olivennes*, in view of *Ziegler*, and further in view of *Hall*, and further in view of *Deghengi* or *Rabasseda*. The inapplicability of *Felberbaum*, *Olivennes*, *Ziegler*, and *Hall* was discussed above. The Examiner cites *Dehgenghi* and *Rabasseda* are cited as teaching specific LHRH antagonists. However, neither

Dehgenghi nor *Rabasseda* relate to the missing teaching, the administration of an LHRH antagonist during a first luteal phase to induce the timing of a second menstrual cycle. Accordingly, *Dehgenghi* and *Rabasseda* fail to cure the deficiencies of *Felberbaum*, or *Olivennes* in view of *Ziegler* and *Hall*.

IX. CONCLUSION

In summary, Appellants submit that the cited art, alone or in combination, does not render the claimed invention obvious. The claims should be allowed.

Respectfully submitted,

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Dated: September 9, 2011 By: /Sheridan Snedden/

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X. CLAIMS APPENDIX – CLAIMS ON APPEAL

1-3. (Cancelled).

4. (Previously Presented) The method of claim 26, wherein said assisted reproduction techniques are carried out during routine operations of laboratories, clinics, hospitals or other assisted reproduction facilities.

5. (Previously Presented) The method of claim 26, wherein said second dose administers cetrorelix.

6. (Previously Presented) The method of claim 26, wherein said second dose administers teverelix.

7. (Previously Presented) The method of claim 26, wherein said second dose administers ganirelix.

8. (Previously Presented) The method of claim 26, wherein said second dose administers antide.

9. (Previously Presented) The method of claim 26, wherein said second dose administers abarelix.

10-15. (Cancelled)

16. (Previously Presented) The method of claim 26, wherein said first dose administers cetrorelix.

17. (Previously Presented) The method of claim 26, wherein said first dose administers teverelix.

18. (Previously Presented) The method of claim 26, wherein said first dose administers ganirelix.

19. (Previously Presented) The method of claim 26, wherein said first dose administers antide.

20. (Previously Presented) The method of claim 26, wherein said first dose administers abarelix.

21. (Previously Presented) The method of claim 28, wherein said follicle stimulating compound is selected from the group consisting of urinary FSH, recombinant FSH, HMG, recombinant LH, or a combination thereof.

22. (Previously Presented) The method of claim 28, wherein said follicle stimulating compound is clomiphene.

23. (Previously Presented) The method of claim 28, wherein said ovarian stimulation is achieved by administration of antioestrogens and gonadotropins.

24. (Previously Presented) The method of claim 28, wherein said ovarian stimulation is achieved by administration of clomiphene and gonadotropins.

25. (Previously Presented) The method of claim 28, wherein said assisted reproduction techniques comprise applying IVF, ICSI, GIFT, ZIFT or intrauterine insemination via sperm injection.

26. (Previously Presented) A method of programming an infertility treatment cycle comprising controlled ovarian stimulation (COS) and assisted reproductive techniques (ART), the method comprising:

determining a luteal phase of a first menstrual cycle in an infertile patient;

administering a first dose regimen of an LHRH antagonist during said luteal phase of said first menstrual cycle, wherein said first dose regimen of LHRH antagonist induces a luteal regression;

terminating said first dose regimen administration prior to the onset of menses;

determining a follicular phase of a second menstrual cycle wherein said second menstrual cycle immediately succeeds said first menstrual cycle;

administering a follicle stimulating compound during said follicular phase, wherein said follicle stimulating compound stimulates ovarian follicle growth;

administering a second dose regimen of said LHRH antagonist during said follicular phase, wherein said second dose regimen of an LHRH antagonist suppresses premature ovulation;

administering HCG thereby inducing ovulation; and

applying assisted reproduction techniques.

27. (Previously Presented) A method of programming an infertility treatment cycle according to Claim 26, wherein said LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abarelix.

28. (Previously Presented) A method of programming an infertility treatment cycle according to Claim 26, wherein said follicle stimulating compound is selected from

the group consisting of urinary FSH, recombinant FSH, HMG, recombinant LH, clomiphene, or a combination thereof.

XI. EVIDENCE APPENDIX

1. Declaration under §1.132 by Dr. Riethmuller-Winzen, inventor, submitted December 13, 2005.

2. R. FELBERBAUM et al., 'Multiple dose protocol for the administration of GnRH-antagonists in IVF: the "Lubeck-protocol"', 10th WORLD CONGRESS ON IN VITRO FERTILIZATION AND ASSISTED REPRODUCTION, May 1997, pp. 397-404.

3. Olivennes et al., The Single or Dual Administration of the Gonadotropin-releasing Hormone Antagonist Cetrorelix in an In Vitro Fertilization-Embryo Transfer Program, 1994, Fertility and Sterility, 62(3), pages 468476.

4. Ziegler et al., Synchronization of Endogenous and Exogenous FSH Stimuli in Controlled Ovarian Hyperstimulation (COH), 1998, Human Reproduction, 13(3), pages 561-564.

5. Hall et al., Variable Tolerance of the Developing Follicle and Corpus Luteum to Gonadotropin-Releasing Hormone Antagonist-Induced Gonadotropin Withdrawal in the Human, 1991, Joumal of Clinical Endocrinology and Metabolism, 72(5), pages 993-1000.

6. U.S. Patent No. 5,470,847.

7. U.S. Patent No. 5,945,128.

8. Rabasseda et al., Drugs of the Future, 24:393-403 (1999).

9. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007).

XII. RELATED PROCEEDINGS APPENDIX

Appellants know of no other related appeals or interferences which will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.